This report is required by law (7 USC 2143). Failure to report according to the regulations can result in an order to cease and desist and to be subject to penalties as provided for in Section 2150.

See reverse side for additional information.

Interagency Report Control No 0180-DOA-AN

UNITED STATES DEPARTMENT OF AGRICULTURE
ANIMAL AND PLANT HEALTH INSPECTION SERVICE

ANNUAL REPORT OF RESEARCH FACILITY
(TYPE OR PRINT)

1. REGISTRATION NO. 93-R-0391 **CUSTOMER NO.** 1737

FORM APPROVED
OMB NO. 0579-0036

2. HEADQUARTERS RESEARCH FACILITY *(Name and Address, as registered with USDA, include Zip Code)*

MEDIMMUNE VACCINES, INC.
297 NORTH BERNARDO AVE
MOUNTAIN VIEW, CA 94043

b6, b7C

3. REPORTING FACILITY (List all locations where animals were housed or used in actual research, testing, teaching, or experimentation, or held for these purposes. Attach additional sheets if necessary.)

FACILITY LOCATIONS*(sites)*

See Attached Listing As #2. above

REPORT OF ANIMALS USED BY OR UNDER CONTROL OF RESEARCH FACILITY *(Attach additional sheets if necessary or use APHIS FORM 7023A)*

A. Animals Covered By The Animal Welfare Regulations	B. Number of animals being bred, conditioned, or held for use in teaching, testing, experiments, research, or surgery but not yet used for such purposes.	C. Number of animals upon which teaching, research, experiments, or tests were conducted involving no pain, distress, or use of pain-relieving drugs.	D. Number of animals upon which experiments, teaching, research, surgery, or tests were conducted involving accompanying pain or distress to the animals and for which appropriate anesthetic, analgesic, or tranquilizing drugs were used.	E. Number of animals upon which teaching, experiments, research, surgery or tests were conducted involving accompanying pain or distress to the animals and for which the use of appropriate anesthetic,analgesic, or tranquilizing drugs would have adversely affected the procedures, results, or interpretation of the teaching, research, experiments, surgery, or tests. *(An explanation of the procedures producing pain or distress in these animals and the reasons such drugs were not used must be attached to this report)*	F. TOTAL NO. OF ANIMALS (Cols. C + D + E)
4. Dogs					0
5. Cats					0
6. Guinea Pigs			52	2	54
7. Hamsters			318	16	334
8. Rabbits					0
9. Non-Human Primates					0
10. Sheep					0
11. Pigs					0
12. Other Farm Animals					0
13. Other Animals					
Ferrets	38	396	1,144	244	1,849
Cotton Rats			85		85

ASSURANCE STATEMENTS

1) Professionally acceptable standards governing the care, treatment, and use of animals, including appropriate use of anesthetic, analgesic, and tranquilizing drugs, prior to, during, and following actual research, teaching, testing, surgery, or experimentation were followed by this research facility.

2) Each principal investigator has considered alternatives to painful procedures.

3) This facility is adhering to the standards and regulations under the Act, and it has required that exceptions to the standards and regulations be specified and explained by the principal investigator and approved by the Institutional Animal Care and Use Committee (IACUC). **A summary of all the exceptions is attached to this annual report.** In addition to identifying the IACUC-approved exceptions, this summary includes a brief explanation of the exceptions, as well as the species and number of animals affected.

4) The attending veterinarian for this research facility has appropriate authority to ensure the provision of adequate veterinary care and to oversee the adequacy of other aspects of animal care and use.

CERTIFICATION BY HEADQUARTERS RESEARCH FACILITY OFFICIAL
(Chief Executive Officer or Legally Responsible Institutional official)
I certify that the above is true, correct, and complete (7 U.S.C. Section 2143)

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DATE SIGNED 7/11/06

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Column E Explanations

Ferrets:

1. Registration number: **93-R-0391**
2. Number of animals used in studies: **244**
3. Species (common name) of animal used in the study: **Ferrets**
4. Explain the procedure producing pain and/or distress.

The 244 ferrets assigned to Block E were used in two different study types: (a) [redacted] research studies and [redacted] FDA mandated [redacted]

(a) [redacted] research studies involve understanding the [redacted] or [redacted] when used in [redacted] susceptible individuals. The ferret is the only laboratory animal model that exhibits clinical signs of [redacted] similar to people and transmits [redacted] naturally to other susceptible ferrets. Therefore, ferrets are the most relevant animal model to use for these studies. In order to mimic the [redacted] state that is relevant in the human population (people undergoing [redacted], having [redacted] o [redacted] patients for example), the ferrets needed to be [redacted] by use of drugs such as [redacted]. The seriously [redacted] state may lead to increased susceptibility to [redacted] and to a general feeling [redacted] **Therefore, these studies have been classified as E. Although there is no pain involved, there is a degree of untreatabl** [redacted] that is being induced by the study. Animals are observed, given supportive care such as food treats and fluids as needed. Any [redacted] are treated with [redacted] products [redacted] such as [redacted] The [redacted] then heal.

(b) [redacted] are mandated by the FDA (see 6. below). Ferrets are [redacted] with the [redacted] or the [redacted] as a positive control and a third group with media only as a negative control. Some of the [redacted] (but not all) will develop clinical signs of [redacted] Only the animals which exhibit a significant [redacted] are classified as ill and therefore are assigned USDA category E. The test runs for 3 days [redacted] to euthanasia of all animals and tissue collection for analysis.

5. Provide scientific justification why pain and/or distress could not be relieved. State methods of means used to determine that pain and/or distress relief would interfere with test results. (For Federally mandated testing, see Item 6 below.)

(a) In [redacted] research studies, analgesics cannot be used for two reasons: many analgesics also have [redacted] effects which include the [redacted] and [redacted] responses which would effect the very physiological functions that are under study – responses of the normal and [redacted] animal to [redacted] Secondly,

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the [redacted] used to induce th[redacted] state is quite toxic to other organs such as the [redacted] Using analgesics and [redacted] might lead to more severe effects on these organs. See attached literature search conducted last spring.

(b) The [redacted] used in the [redacted] is a positive control against which are measured [redacted] and performance of the [redacted] The use of analgesics in these animals would invalidate this assessment.

6. What, if any, federal regulations require this procedure? Cite the agency, the Code of Federal Regulations (CFR) title number and the specific section number (e.g., APHIS, 9 CFR 113.102):

For (b) above:

Agency: Food and Drug Administration (FDA) 21 CFR 610.1

"No lot of any licensed product shall be released by the manufacturer prior to the completion of tests for conformity with the standards applicable to such product. Each applicable test shall be made on each lot after completion of all processes of manufacture which may affect compliance with the standard to which the test applies."

Guinea Pigs:

1. Registration number: **93-R-0391**
2. Number of animals used in studies: **2**
3. Species (common name) of animal used in the study: **Guinea pigs**
4. Explain the procedure producing pain and/or distress:

Guinea pigs are used to determine whether [redacted] are present in the tissue culture medium used to grow [redacted] lots for [redacted] use. The animals are injected with [redacted] of the medium [redacted] and observed for up to 42 days for signs of [redacted] If signs of ill health are noted, the animal is immediately euthanatized and tissues taken to determine if there is a [redacted] present. This protocol is classified as E since there is a chance of pain and distress but retrospective classification indicated that of the animals tested, only two exhibited signs o[redacted]. They were euthanatized immediately.

5. Provide scientific justification why pain and/or distress could not be relieved. State methods of means used to determine that pain and/or distress relief would interfere with test results. (For Federally mandated testing, see Item 6 below.)

Justification for conducting this test is that guinea pigs are very susceptible to [redacted] by many [redacted] that might contaminate the tissue culture medium. They are also large enough to enable an enhanced chance of detection since greater quantities [redacted]

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[redacted] used in mice for a similar [redacted]. The medium must pass other *in vitro* testing successfully prior to this final *in vivo* test for purity. Minimum numbers are used per test and since [redacted] are not expected, only a very few animals experience any pain or distress at all in this test. Those that do exhibit signs of illness, are not treated with analgesics but are euthanatized right away as soon as signs of [redacted] or [redacted] are noted.

6. What, if any, federal regulations require this procedure? Cite the agency, the Code of Federal Regulations (CFR) title number and the specific section number (e.g., APHIS, 9 CFR 113.102): **None**

This study was performed to examine research [redacted] and so was not an FDA mandated test for product but [redacted] for research testing purposes.

Hamsters

1. Registration number: **93-R-0391**
2. Number of animals used in studies: **16**
3. Species (common name) of animal used in the study: **Hamsters**
4. Explain the procedure producing pain and/or distress.

Hamsters [redacted] with drugs such as [redacted] to enable the enhanced replication of the [redacted] candidate [redacted] and control [redacted] for study purposes. [redacted] may lead [redacted] and [redacted]. The [redacted] may lead to symptoms of a [redacted] such as [redacted] an [redacted] and [redacted] and [redacted]

5. Provide scientific justification why pain and/or distress could not be relieved. State methods of means used to determine that pain and/or distress relief would interfere with test results. (For Federally mandated testing, see Item 6 below.)

Hamsters are [redacted] to study [redacted] in [redacted] host. Hamsters are the phylogenetically lowest laboroatory animal species that is permissive for [redacted] They are not available as genetically [redacted] and therefore must be made [redacted] via drugs to produce the [redacted] state to mimic that which is relevant in the human population (people undergoing [redacted] having [redacted] or [redacted] for example. The seriously [redacted] state may lead to increased susceptibility t[redacted] and to a general feeling of [redacted]. **Therefore, these studies have been classified as E. Although there is no pain involved, there is a degree of** [redacted] that is being induced by the study. Animals are observed, given supportive care such as food treats and fluids as needed. Hamsters typically do not exhibit many signs of illness when

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chemically [redacted]. Any [redacted] are treated with [redacted] products topically such as [redacted] The [redacted] then heal.

6. What, if any, federal regulations require this procedure? Cite the agency, the Code of Federal Regulations (CFR) title number and the specific section number (e.g., APHIS, 9 CFR 113.102): **None**

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Literature Search

[redacted] models of [redacted]

Search conducted: 18Feb2006
Dates covered: Unlimited to 18Feb2006
Key words: [redacted]
alternative
Databases evaluated: AGRICOLA, Entrez_PubMed

[redacted]

MedImmune Vaccines, Inc.

Dr. R. Ridenour, VMO
USDA – APHIS
Animal Care
Western Region
2150 Centre Ave.
Building B, Mail Stop 3W11
Ft. Collins, CO 80526

16FEB07

RE: 93-R-0391 Annual Report FY 2006 – Request for Additional Information dated 29JAN07

Dear Dr. Ridenour,

Here is our response to your request for more details concerning entries in Column E on our FY 2006 Annual Report.

Guinea Pigs (2)

- **Please explain how the use of pain and/or distress relieving drugs would have adversely affected the progress, outcome, and/or interpretation of the test/study.**

Guinea pigs are specified by two government bodies as the species of choice for relevant safety testing. In our annual report, we did not specify these tests as being required by government regulations since the tests were performed in-house and not conducted under strict GLP regulations. However, the testing was being done for [redacted] a *GLP-like* study. It was expected that the test articles to be evaluated would be free of [redacted] as they would have passed *in vitro* tests before use *in vivo*. However, in the case where [redacted] are present, signs reflecting morbidity or mortality, such [redacted] may occur. The use of analgesics may mask these effects and thus mask the presence of an [redacted]. Hence, analgesics could not be used in this test. Likewise, the other reason for safety testing of biological materials *in vivo* is to ensure that adverse events do not occur due to unanticipated biological responses (i.e. [redacted] provoked by [redacted]. For the same reason, if analgesics are given then the adverse event may be suppressed or masked and not detected.

As reported, during the course of this testing, two animals did appear to be experiencing pain or distress and were not given analgesics for the reason stated above and as per IACUC approved protocol.

Relevant federal regulations: (1) The Center for Biologics Evaluation and Research (CBER), United States Food and Drug Administration, in the 1993 "Points to Consider in the Characterization of Cell Lines Used to Produce Biologicals." (2) General Safety 21CFR610.11

Hamsters (16)

- **Please explain why the [redacted] was untreatable and how the use of pain and/or distress relieving drugs would have adversely affected the progress, outcome, and/or interpretation of the test/study.**

The study was performed at the request of the FDA to verify the replication [redacted]. The [redacted] and the [redacted] do not grow well in animal models – the rodent (cotton rat) and hamster model chosen for this study support the best replication. The product being tested [redacted] is intended to be given to a neonatal infant population which has a [redacted] In order to better understand the tissues and kinetics [redacted] in a model which duplicates the young infant, these animals needed to be [redacted]. The [redacted] itself does not cause pain or distress to the animals. The [redacted] egimen does appear to cause some degree of [redacted] in some animals as observed by either a [redacted] animal or one that does not eat or drink as much. This kind of [redacted] is not treatable except by ceasing treatment which would then invalidate the study goal, in other words the animal would no longer be [redacted]. People undergoing [redacted] often do not feel very well. If they feel [redacted] they may take [redacted] There is not much they can do either since they are not feeling pain per se [redacted] for which [redacted] medications might be useful. Some of the other undesirable outcomes of [redacted] are [redacted] of the [redacted] or other system which are treated by antibiotics. In the hamster, the only [redacted] that has been seen was at the [redacted] site. These were treated by topical antibiotics and resolved.

If a mouse or rat model would have supported [redacted] then [redacted] model might have been used such as the [redacted] However these animals do not support thi[redacted] so could not be used.

In fact, the classification of this protocol as category E may be incorrect in the hamster. The protocol was approved as a pilot study (using only 16 animals) and was categorized as E due to the fact that people undergoing [redacted] may not feel very well and also from our experience with another chemically [redacted] – the ferret. The ferret does appear to feel unwell when [redacted] with a similar regimen. The ferret will become [redacted] and not [redacted] normally for a time. It then will appear to recover after a few days. The hamster, however, shows no [redacted], maintains its activity, grooming and eating/drinking patterns and from our observations during this pilot protocol, they do not, in fact, appear to be experiencing any pain or distress.

Our veterinarian has contacted Ms. Linda Kovar by telephone as instructed in the cover letter to request guidance on this matter.

Please contact our [redacted] if you have further questions.

[redacted]

MedImmune

[redacted]